Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 5351

Synthesis and reactivity of 5-polyfluoroalkyl-5-deazaalloxazines†

Sergii Dudkin,[a] Viktor O. Iaroshenko,*[a,b] Vyacheslav Ya. Sosnovskikh,[c] Andrey A. Tolmachev,[b,d] Alexander Villinger[a] and Peter Langer*[a,e]

Received 19th September 2012,
Accepted 13th June 2013

DOI: 10.1039/c3ob26837c

www.rsc.org/obc

Reaction of 6-arylamino-1,3-dialkyluracils with anhydrides of polyfluorocarboxylic acids in the presence of pyridine and subsequent cyclization with concentrated H_2SO_4 gave the corresponding 1,3-dialkyl-5-(polyfluoroalkyl)pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones (5-polyfluoroalkyl-5-deazaalloxazines). The reactivity of these compounds towards nucleophilic reagents, such as sodium cyanoborohydride, acetophenone, nitromethane, potassium cyanide, indole and *p*-thiocresol, as well as Suzuki and Sonogashira couplings are described. The nucleophilic addition takes place at the 5-position of the 5-deazaalloxazine system and is in many cases irreversible to give 5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione derivatives in good to excellent yields.

Introduction

Heterocyclic scaffolds, containing polar groups capable of hydrogen bond formation, are of high relevance for drug design as basic structural platforms for the development of tightly binding enzyme ligands, enzyme pitfalls and suicide substrates.[1] To date, several dozens of such compounds have been reported; among them are bioactive molecules and drugs.[1–3] Pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (also known as 5-deazaflavins or 5-deazaisoalloxazines, **I**), where N-5 of the naturally occurring flavins (isoalloxazines, **II**) is replaced by CH, have been studied extensively in both enzymatic and model systems to provide mechanistic insight into flavin-catalysed reactions.[4] In addition, the 5-deazaflavins **I** can be considered structurally as a model not only of flavin nucleotides, but also of nicotinamide nucleotides protected by annelation, since they oxidize simple alcohols under alkaline conditions to the corresponding carbonyl compounds and they are themselves hydrogenated to 1,5-dihydro-5-deazaflavins.[5] The 5-position of the 5-deazaflavin ring system **I** is very π-electron deficient and the reactions of these compounds with nucleophiles start predominantly with attack at the unsubstituted C-5 atom.[6]

Introduction of a trifluoromethyl group into bioactive molecules, especially in the positions responsible for their physiological profile, has become an important aspect of pharmaceutical research owing to the unique physical and biological properties of fluorine.[7] Now it is well known that a trifluoromethyl group can have profound and unexpected results on biological activity and reactivity of the derived fluorinated compounds.[8] Recently, the strong electrophilic feature of the CF_3 group was used to design a set of protease inhibitors.[3] Very recently, we applied the concept illustrated above to develop several types of 2-R^F- and 6-R^F-functionalized purines, purine isosteres as well as their corresponding nucleosides.[9] These compounds are potential inhibitors of two biologically relevant *de novo* purine bio-synthesis enzymes, namely adenosine deaminase (ADA)[10] and inosine monophosphate dehydrogenase (IMPHD).[11]

We envisaged that introduction of such powerful electron-withdrawing substituents like R^F groups into the 5-position of pyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones (5-deazaalloxazines, **III**), which are closely related to pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-diones (5-deazaisoalloxazines, **I**), would increase their reactivity toward nucleophilic reagents and open up a broad synthetic scope of this important nitrogen-containing heterocyclic system. Unlike previously known 5-deazaalloxazines **III**,[12] selectively fluorinated pyrimido[4,5-*b*]quinolines **IV** have not received much attention, despite their potential interest as highly reactive substrates in organic synthesis for the construction of a wide range of novel 5-deazaalloxazine

[a]*Institut für Chemie, Universität Rostock, Albert Einstein Str. 3a, 18059 Rostock, Germany. E-mail: peter.langer@uni-rostock.de; Fax: +0049 381 498 6412; Tel: +0049 381 498 6410*
[b]*National Taras Shevchenko University, 62 Volodymyrska Str., 01033 Kyiv, Ukraine*
[c]*Department of Chemistry, Ural Federal University, 51 Lenina Ave., 620000 Ekaterinburg, Russia*
[d]*Enamine Ltd, Alexandra Matrosova Street 23, Kyiv 01103, Ukraine*
[e]*Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert Einstein Str. 29a, 18059 Rostock, Germany*

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of all compounds. CCDC 895395–895401, 934983. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob26837c

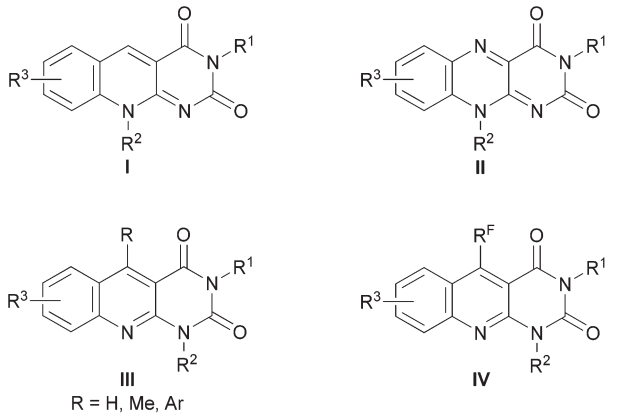


Fig. 1 5-Deazaflavins **I**, flavins **II** and 5-deazaalloxazines **III** and **IV**.

derivatives with interesting biological activities and useful physicochemical applications (Fig. 1). Of particular interest is the development on the basis of fluorescent nucleosides that maintain the hydrogen-bonding properties of natural nucleoside bases.[13]

5-Deazaisoalloxazines **I** and 5-deazaalloxazines **III** (R = H) have previously been synthesized by cyclization of 6-arylamino-1,3-dimethyluracils with one-carbon reagents (triethyl orthoformate, dimethylformamide dimethylacetal, carbon disulfide, and the Vilsmeier reagent).[14] Similarly, treatment of 6-arylamino-1,3-dimethyluracils with aromatic aldehydes provided 5-aryl-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*,5*H*,10*H*)-diones, which were subsequently dehydrogenated with thionyl chloride to give 5-aryl-1,3-dimethylpyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **III** (R = Me, Ar).[15,16] The three-component condensation between barbituric acids, anilines and aldehydes is an excellent and convenient approach, provided that the corresponding aldehyde is readily available.[10] At the same time, examples of the synthesis of 5-R^F-5-deazaalloxazines **IV** are lacking, a fact which prompted us to investigate their preparation and reactivity. Derivatives of polyfluorinated acids are commercially available and relatively inexpensive as compared to the corresponding aldehydes, which is the reason why we decided to utilize them in the 5-R^F-5-deazaalloxazine synthesis.

When the presence of a perfluorinated residue is required in a bioactive target molecule, either the fluoroalkylation reaction of a convenient intermediate or the synthesis from a perfluoroalkyl substituted precursor may be employed.[7] If the latter approach is used, a perfluoroacylated reagent is often employed as the electrophilic species for the synthesis of R^F-containing building blocks.[17] Herein, we report that a perfluoroalkyl chain can be introduced at C-5 of 5-deazaalloxazines **III** by reaction of 6-arylamino-1,3-dimethyluracils with polyfluorocarboxylic acid anhydrides or chlorides and subsequent cyclization mediated by concentrated sulfuric acid. This is a general synthesis of novel 5-R^F-5-deazaalloxazines **IV** which possess interesting chemical and physical properties.

Results and discussion

The requisite starting materials, 6-anilino-1,3-dialkyluracils **2**, were prepared by nucleophilic displacement of commercially available 6-chloro-1,3-dimethyluracil with the appropriate arylamines according to the reported procedures (Table 1).[15,17,18] 6-Chloro-1,3-dipropyluracil **1b**, the starting material for 1,3-dipropyl-5-deazaalloxazines **4s** and **4t**, was prepared from *N*,*N*′-dipropylurea and malonic acid in two steps and 54% overall yield.[19] Coupling reactions with anilines were carried out in most cases at 180 °C.[15] In the case of tetrahydroquinoline, 5-amino-3-methyl-1-phenylpyrazole and α-naphthylamine, the use of *n*-butyllithium as a base was necessary.[18]

In our initial study we have obtained a series of 6-anilino-5-(polyfluoroacyl)-1,3-dialkyluracils **3** starting from easily accessible 6-anilino-1,3-dialkyluracils **2** by a usual polyfluoroacylation procedure.[17] It was found that treatment of uracils **2** with the corresponding polyfluorinated carboxylic acid anhydride (or acid chloride, if R^F = *n*-C_3F_7), carried out in dioxane at room temperature in the presence of pyridine (1.2 equiv.), resulted in the formation of 6-anilino-5-(polyfluoroacyl)-1,3-dimethyluracils **3a–x** in excellent yields (79–99%). In most cases, the reaction was complete after 10–12 h and the products could be isolated by solvent evaporation, followed by trituration with water and simple filtration of the precipitate formed (Scheme 1). The results are summarized in Table 2. Derivatives **3k,l,s** were not isolated in pure form, because we faced difficulties with crystallization, whereas compound **3x** simultaneously cyclizes immediately after its formation. As can be seen from Table 2, this reaction has virtually no limitations with regard to the nature of the polyfluoroalkyl group or the nature and position of the substituent in the aniline ring. Although the chemistry of uracils has been well documented,[4–6] compounds **3** have hitherto not been reported.

It is important to note that similar reactions of 6-(4-anisidino)-1,3-dipropyluracil **2j**, 6-(1-naphthylamino)-1,3-dimethyluracil **2m**, 6,6′-[biphenyl-4,4′-diyldi(imino)]bis(1,3-dimethyluracil) **2k**, and 6,6′-[methylenebis(4,1-phenyleneimino)]bis(1,3-dimethyluracil) **2l** gave the corresponding compounds **3t–w** (Table 2). These results clearly show that the present reaction could be applicable to various types of 6-arylamino-1,3-dialkyluracils **2**, providing a simple and rapid route to the synthesis of a wide range of the polyfluoroacylated uracil derivatives **3**, which are precursors for the preparation of 5-R^F-5-deazaalloxazines **4**. The structures of products **3** were established from satisfactory analytical and spectroscopic data and, in particular, by the presence of the characteristic quartet or triplet of the carbonyl carbon atom connected to the R^F group in their ^{13}C NMR spectra.

When the corresponding uracil **3** was dissolved in concentrated H_2SO_4 and allowed to stand at room temperature for 3 h, 5-R^F-5-deazaalloxazines **4a–x** were obtained in good to excellent yields (49–92%). In the case of a *meta*-substituted aniline residue, regioselective cyclization took place yielding mainly the 8-substituted 5-deazaalloxazines **4k–n**. Electrophilic

Table 1 Yields of 6-amino-1,3-dialkyluracils **2a–s**

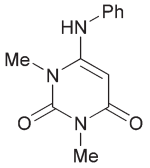
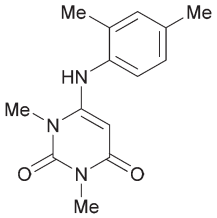
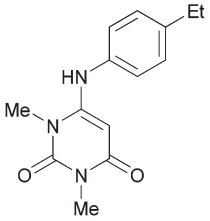
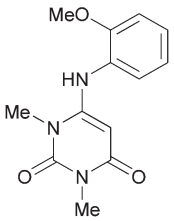
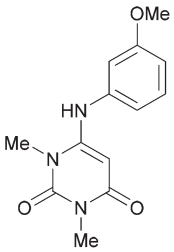
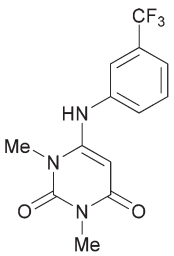
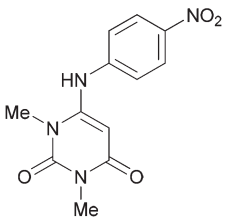
Structure[a]	Yield **2**[b] (%)	Method[c]
	**2a** (79)	A
	**2b** (71)	A
	**2c** (75)	A
	**2d** (64)	A
	**2e** (85)	A
	**2f** (84)	A
	**2g** (35)	A

Table 1 *(Contd.)*

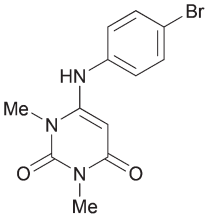
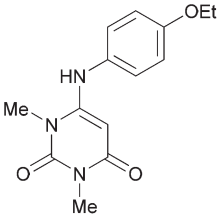
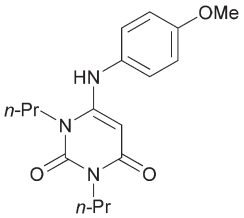
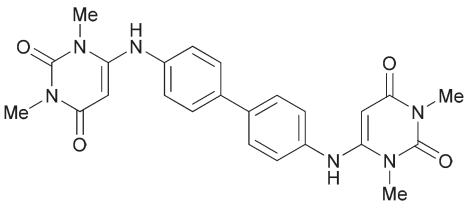
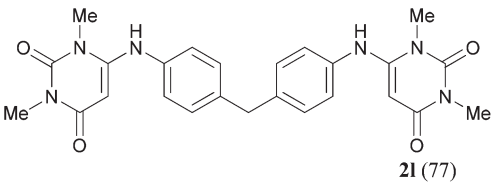
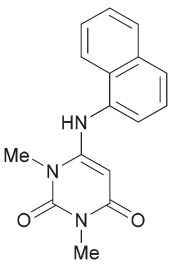
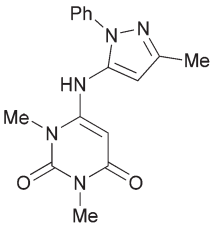
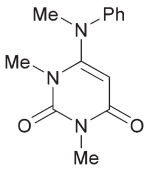
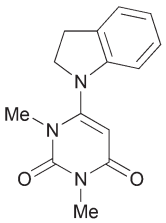
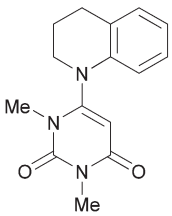
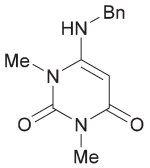
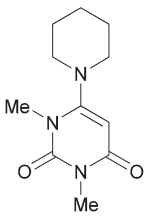
Structure[a]	Yield **2**[b] (%)	Method[c]
	**2h** (70)	A
	**2i** (76)	A
	**2j** (69)	A
	**2k** (91)	B
	**2l** (77)	B
	**2m** (69)	C
	**2n** (82)	C

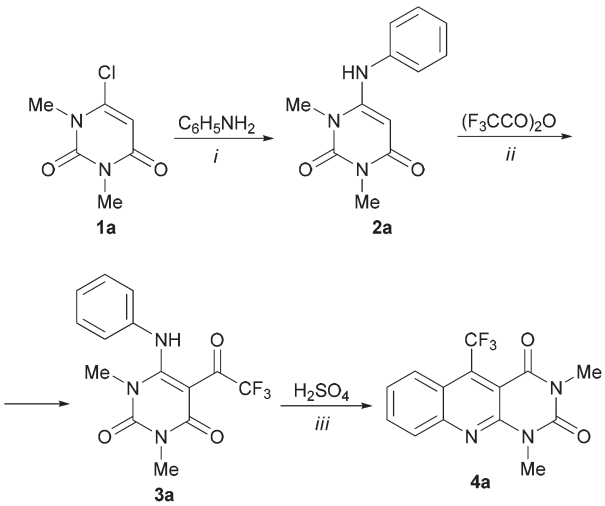
Table 1 *(Contd.)*

Structure[a]	Yield 2[b] (%)	Method[c]
	**2o** (56)	A
	**2p** (69)	A
	**2q** (87)	C
	**2r** (87)	D
	**2s** (98)	E

[a] These compounds, except examples **2f,j–l,n,p,q**, have been previously described in the literature. [b] Yields refer to pure isolated products. [c] Method A: 6-chloro-1,3-dialkyluracil **1a** or **1b** (1 equiv.), arylamine (2.2 equiv.), 180 °C, 3 h, under argon; method B: **1a** (1 equiv.), arylamine (0.8 equiv.), quinoline, 180 °C, 3 h, under argon; method C: arylamine (2.2 equiv.), *n*-BuLi, THF, −78 to 20 °C, under argon; method D: **1a**, benzylamine, triethylamine, dioxane, boiling under reflux, 10 h; method E: 1a, piperidine, dioxane, 100 °C, 2 h.

attack of the less sterically hindered position leads to predomination of the 8-substituted isomer. On the other hand, hydrophobic interaction can take place between the substituent attached to the aniline ring and the polyfluoroalkyl group. This balance between attraction and repulsion is supposed to be decisive for the observed regioisomeric ratio.

The 8-methoxy isomers **4k,l** were prepared in low yields by a combined procedure including the reaction of uracil **2e** with trifluoro- and chlorodifluoroacetic anhydride, respectively, and subsequent treatment of the crude products with sulfuric acid, followed by a proper recrystallization from methanol (Table 2). Purification of **4m,n** required a recrystallization. A similar result was obtained with uracils **3t–w** under the same



Scheme 1 Synthetic route to 5-polyfluoroalkyl-5-deazaalloxazines exemplified for the synthesis of **4a**. *Reagents and conditions*: *i*: arylamine (2.2 equiv.), 180 °C, 3 h, under argon; *ii*: pyridine, dioxane, 20 °C, overnight; *iii*: concd H_2SO_4, 20 °C, 3 h.

conditions, which gave compounds **4t–w** in 46–81% yields. Pyrazolopyridopyrimidine **4x** was prepared in 75% yield directly from **2n**, which cyclizes immediately during the trifluoroacetylation reaction (**3x** could not be isolated). The structures of **4j,m,q** were confirmed by X-ray crystal structure analysis (see ESI, Fig. 1–3†).[20]

Products **5a** and **5b** were prepared by perfluoroacylation of 6-aminouracils **2p** and **2q**, respectively (Scheme 2). Product **5c–e** was prepared by reaction of **2o**, **2r** and **2s** with trifluoroacetic anhydride. The reaction of **5a–c** with sulfuric acid provided the 5-hydroxy-5,10-dihydro-5-deazaflavins **6a–c** in high yields (72–94%). The analogous reactions of **5d,e** failed, due to decomposition. Treatment of compounds **6a,b** with thionyl chloride resulted in the formation of 5-deazaalloxazines **7a,b** which possess an ω-chloroalkyl group at the 9-position. The formation of **7a,b** can be explained by aromatization and ring cleavage by attack of a thionyl chloride derived chloride anion to the position next to the nitrogen atom (nucleophilic substitution). This reaction is irreversible which is understandable based on our observation that flavin **4b** did not undergo methylation with methyl iodide or dimethyl sulphate (xylene, 150 °C; no reaction was observed). The structures of **6a** and **7a** were confirmed by X-ray single crystal analysis (see ESI, Fig. 4 and 5†).[20]

To further study this observation, we followed the reaction of **6a** with triflic anhydride by NMR. Addition of triflic anhydride to **6a**, dissolved in a mixture of $CDCl_3$ and CD_2Cl_2, resulted in the formation of 5-deazaalloxazine **6′a**, which was observed by ^1H and ^{13}C NMR. The CH_2-protons appear as two triplets which prove the equivalence of the protons within each methylene group and, consequently, the molecular symmetry as the methylene groups are located in the mirror plane. In the opposite case, it can be expected that the pattern of the signals would be more complicated, namely four doublets of doublets of doublets.

Table 2 Yields of 6-arylamino-5-(polyfluoroacyl)uracils **3a–w** and 5-polyfluoroalkyl-5-deazaalloxazines **4a–x**

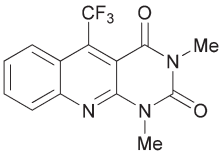
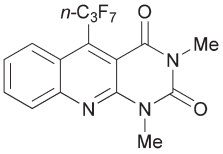
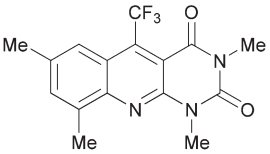
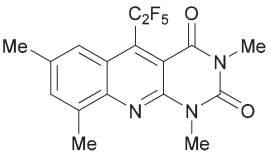
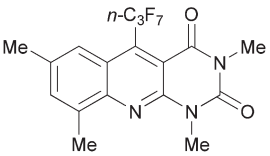
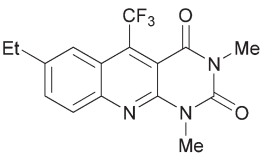
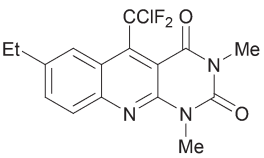
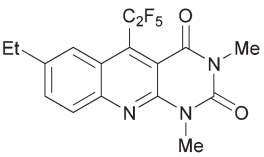
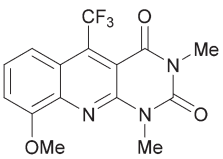
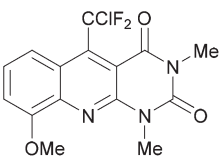
Starting material	Yield[a] (%)		Structure of **4**
2a	**3a** (93)	**4a** (89)	
	3b (96)	**4b** (73)	
2b	**3c** (90)	**4c** (84)	
	3d (88)	**4d** (84)	
	3e (87)	**4e** (92)	
2c	**3f** (88)	**4f** (50)	
	3g (97)	**4g** (57)	
	3h (94)	**4h** (81)	
2d	**3i** (90)	**4i** (49)	
	3j (92)	**4j** (67)	

Table 2 *(Contd.)*

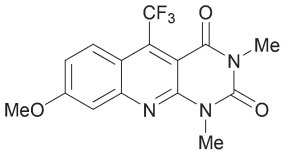
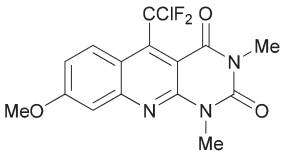
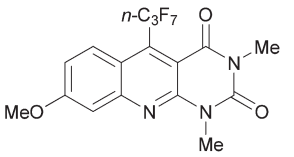
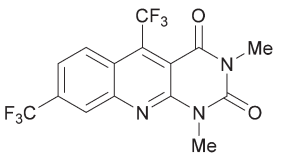
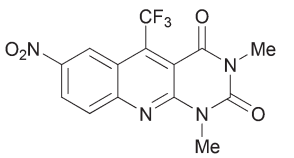
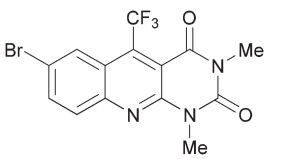
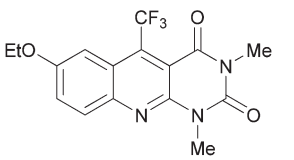
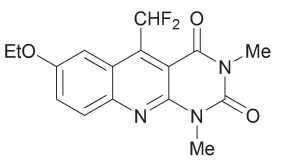
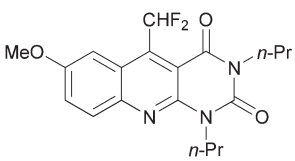
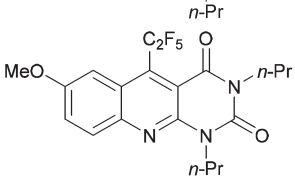
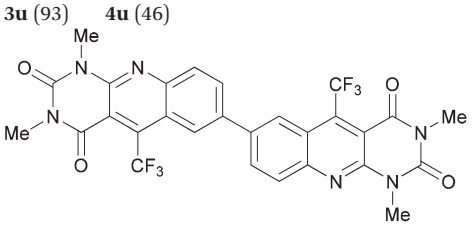
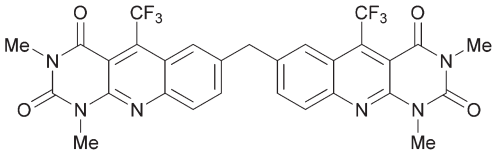
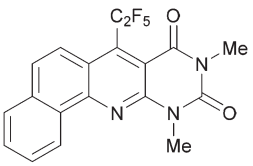
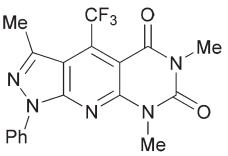
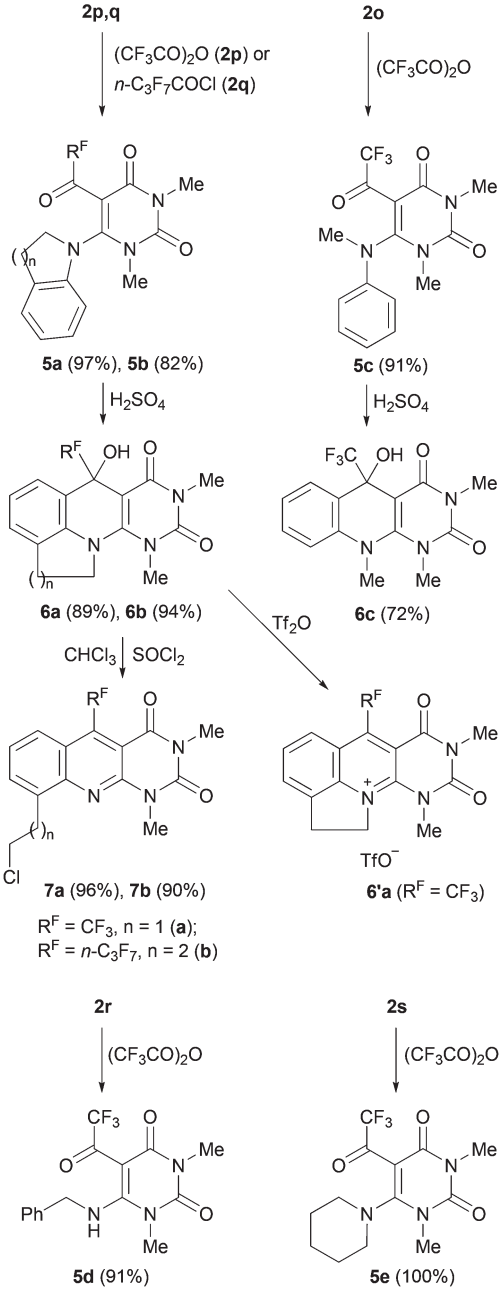
Starting material	Yield[a] (%)		Structure of **4**
2e	—	**4k** (12)[b] 87/13[d]	
	—	**4l** (40)[b] 92/8[d]	
	3m (94)	**4m** (32) 50/50[d]	
2f	**3n** (99)	**4n** (51) 86/14[d]	
2g	**3o** (79)	**4o** (82)	
2h	**3p** (94)	**4p** (84)	
2i	**3q** (82)	**4q** (73)	
	3r (99)	**4r** (80)	
2j	—	**4s** (86)[b]	
	3t (86)	**4t** (81)	

Table 2 *(Contd.)*

Starting material	Yield[a] (%)	Structure of **4**
2k	**3u** (93) **4u** (46)	
2l	**3v** (98) **4v** (51)	
2m	**3w** (86) **4w** (54)	
2n	**3x** (0)[c] **4x** (75)[c]	

[a] Yields refer to pure isolated products. [b] Yield after 2 steps (the product of acylation was introduced into the reaction without purification). [c] After acylation, product **4x** was directly isolated. [d] Ratio of 8/6-substituted isomers.

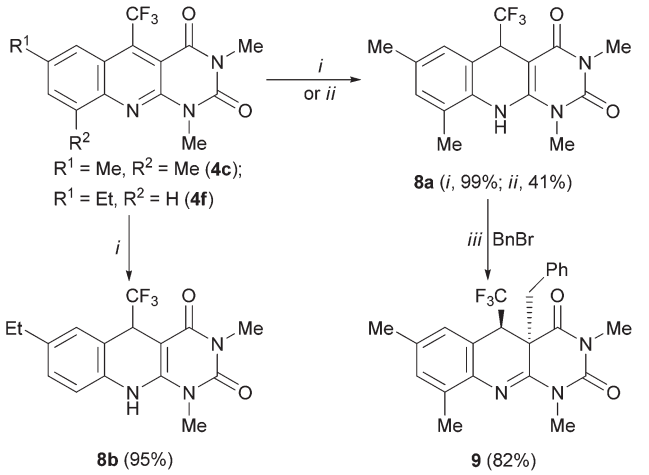


Scheme 2 Synthesis of compounds **5a–e**, **6a–c** and **7a,b**.

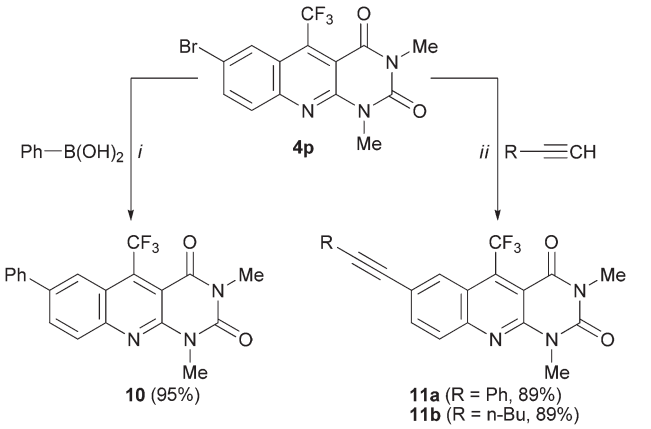
5-R^F-5-deazaalloxazines **4** and **7** show an enhanced reactivity at their 5-position, due to the presence of the perfluoroalkyl group. Therefore, these molecules are promising starting materials for reactions with nucleophiles. The reaction of **4c,f** with sodium cyanoborohydride[21] gave 5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-diones **8a,b** in almost quantitative yields (Scheme 3). The structure of **8a** was independently confirmed by X-ray diffraction analysis (see ESI, Fig. 6†).[20] Compound **8a** could also be successfully prepared from diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, albeit under more rigorous conditions and in lower yield (41%). The reaction of **8a** with benzyl bromide afforded the *trans*-configured benzylated derivative **9** (Scheme 3). The structure of the product was independently confirmed by X-ray crystal structure analysis (see ESI, Fig. 7†).

The Suzuki reaction of 7-bromo-5-deazaalloxazine **4p** with phenylboronic acid, carried out using K_2CO_3 and $Pd(PPh_3)_4$ in dioxane and water at 100 °C,[22] resulted in the formation of product **10**. The Sonogashira coupling of **4p** with terminal acetylenes, in the presence of $Pd(PPh_3)_2Cl_2$, CuI and diisopropylamine in THF,[23] gave compounds **11a,b** in high yields (Scheme 4).

To demonstrate the ability of compounds **4** to undergo nucleophilic addition reactions, 5-deazaalloxazine **4f** was allowed to react with acetophenone, nitromethane and potassium cyanide (Scheme 5). We found that **4f** smoothly reacted with these reagents under basic conditions to produce the expected products **12a–c** in excellent yields (81–94%). The conjugate addition of indole also took place, in the presence of sodium hydride under mild conditions, to give product **12d**. The reaction proceeded under kinetic reaction control with very good regioselectivity in favour of the attack of the nitrogen (rather than the carbon) atom of indole. The addition of a small amount of acetic acid proved to stabilize the *N*-substituted adduct **12d**, but it can also be readily cleaved to give the starting materials upon heating in the presence of trace



Scheme 3 Reduction of 5-deazaalloxazines **4c,f** and benzylation of **8a**. *Reagents and conditions*: *i*: $NaBH_3CN$, THF, AcOH, 4 days; *ii*: diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (6 equiv.), xylene, TsOH, 155 °C, 5 h, under argon; *iii*: K_2CO_3, DMF, 20 °C, overnight, under argon.

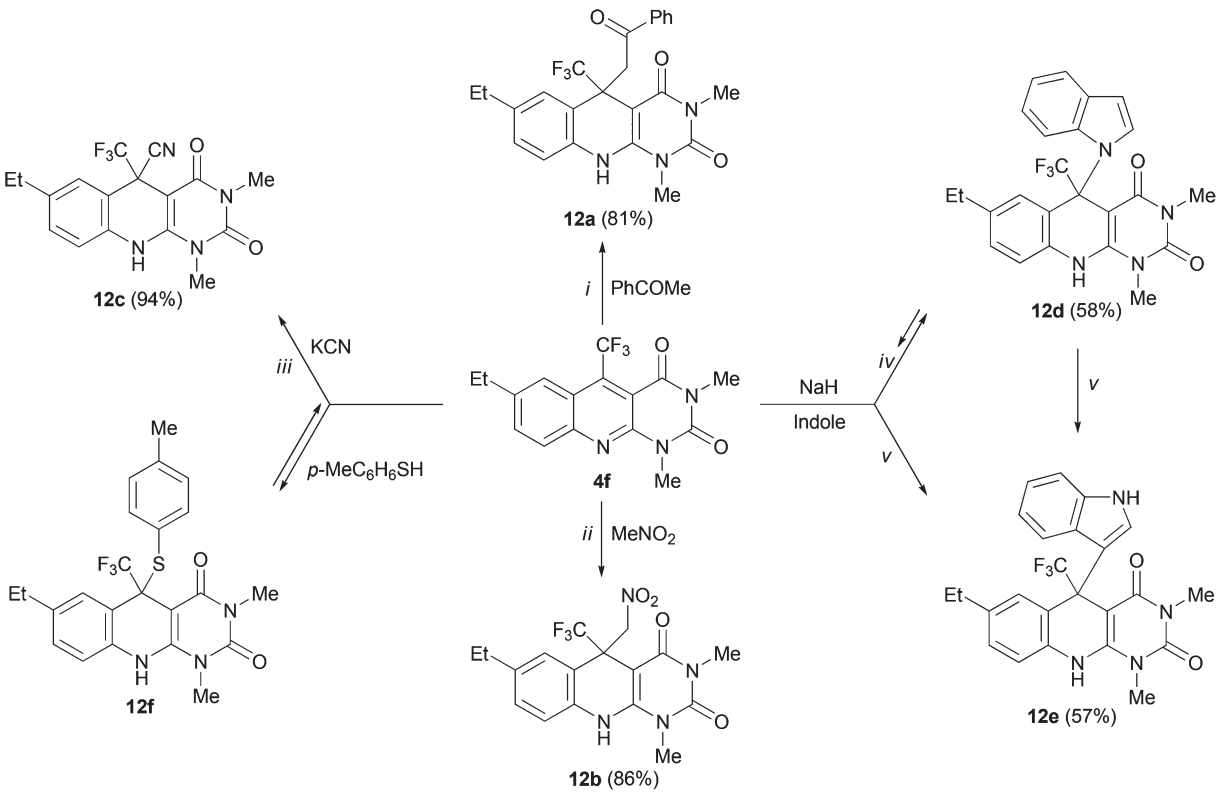


Scheme 4 Suzuki and Sonogashira coupling reactions of 7-bromo-5-deaza-alloxazine **4p**. *Reagents and conditions*: *i*: $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, 100 °C, 0.5 h, under argon; *ii*: $Pd(PPh_3)_2Cl_2$, CuI, $HN(iPr)_2$, THF, 20 °C, 48 h, under argon.

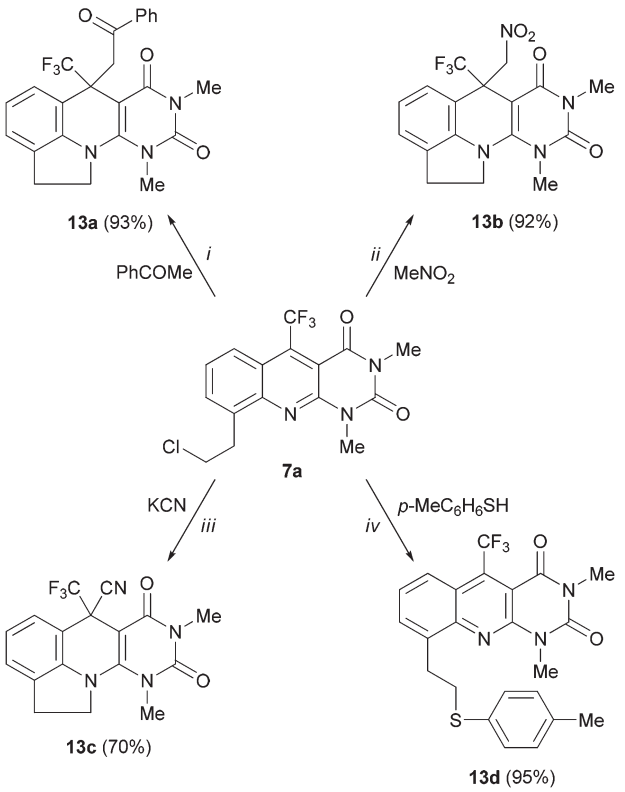
amounts of a base. The *N*-substituted adduct **12d** underwent a rearrangement at 80 °C to form the thermodynamically more stable *C*-substituted isomer **12e.** The latter can be prepared directly by reaction of **4f** with indole under the same conditions in 57% yield.

The reaction of 5-deazaalloxazine **4f** with *p*-thiocresol is reversible. The equilibrium is shifted almost completely towards product **12f,** which was observed by TLC. However, **12f** could not be isolated, because of its decomposition during the isolation. In the case of the reaction of **5f** with morpholine, no product could be detected even when sodium hydride was added as a catalyst. Therefore, we assume that the equilibrium is strongly shifted towards the starting materials (Scheme 5).

The reaction of **7a,** containing a pendent chloroethyl group, with acetophenone, nitromethane and potassium cyanide



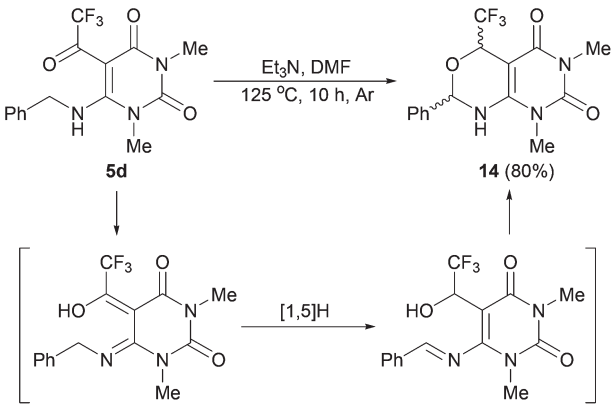
Scheme 5 Reactions of 5-deazaalloxazine **4f** with *C*- and *S*-nucleophiles. *Reagents and conditions*: *i*: NaH, THF, 20 °C, overnight; *ii*: NaOMe, THF, MeOH, 20 °C, overnight; *iii*: DMSO, 20 °C, overnight; *iv*: NaH, THF, 20 °C, 5 min; *v*: NaH, DMF, 80 °C, 5 h, under argon.



Scheme 6 Reactions of 5-deazaalloxazine **7a** with *C*- and *S*-nucleophiles. *Reagents and conditions*: *i*: NaH, THF, 20 °C, overnight; *ii*: NaOMe, THF, MeOH, 20 °C, overnight; *iii*: DMSO, 20 °C, overnight; *iv*: NaOMe, DMF, 20 °C, overnight.

afforded, under the same conditions, products **13a–c** in high yields (70–93%) (Scheme 6). This transformation can be rationalized by initial nucleophilic addition of the nucleophile to position C-5 of the flavin, accompanied by intramolecular nucleophilic substitution of chlorine. Thus, flavins **7a** and **4f** show the same type of reaction with nucleophiles. This can be explained by the fact that the electron-withdrawing R^F group enhances the electrophilicity of the C-5 atom and supports a nucleophilic addition at this position. This effect results in the fact that position 5 of compound **7a** is more reactive towards nucleophiles as the CH_2 carbon atom located next to the chloride group. In contrast, the reaction of **7a** with *p*-thiocresol (in the presence of NaOMe in DMF) followed the normal path and gave deazaalloxazine **13d** by simple nucleophilic substitution in 95% yield. The formation of products **13a–d** can be explained based on the HSAB principle. The soft sulfur nucleophile results in direct attack on the soft alkyl chloride moiety while the more hard carbon nucleophiles attack at the other position located next to the polyfluoro group.

The reaction of 6-(benzylamino)-1,3-dimethyl-5-(trifluoroacetyl)uracil (**5d**) with triethylamine in DMF afforded product **14** as a 7 : 1 mixture of diastereomers (while the *trans*-isomer is the major one) (Scheme 7). Both isomers crystallize together. Therefore, it was not possible to separate them by recrystallization as even a single crystal contained both isomers. The stereochemistry was established by X-ray crystallographic



Scheme 7 Synthesis of compound **14**.

analysis (see the ESI, Fig. 8†).[20] The formation of 1,3-oxazine **14** can be rationalized by a [1,5] hydrogen shift, followed by nucleophilic addition of the hydroxy group to the imino function.

Previously, this unexpected redox reaction was observed in the case of trifluoroacetylated 1-(3,4-dihydro-1-naphthalenyl)-pyrrolidine and 1-(3,4-dihydro-1-naphthalenyl)piperidine.[24] But our example differs from the reactions described in the literature. To the best of our knowledge, no similar reactions with secondary amines have been reported to date. In fact, only reactions involving tertiary amines were reported. This phenomenon is strongly associated with the so-called *tert*-amino effect. Secondly, these reactions proceed mostly either under acidic catalysis (TFA,[25] silica gel,[26] $Sc(OTf)_3$ [27]) or at high temperature,[28] but never in basic media.

Conclusions

Our results related to hitherto unknown 5-R^F-5-deazaalloxazines are of current importance for our ongoing research program related to the design and synthesis of suicide substrates for adenosine deaminase (ADA) and inosine 5-monophosphate dehydrogenase (IMPHD). Their high C-5 reactivity towards nucleophiles and their structural similarity to several biologically relevant compounds, for instance their isosterism to flavins, make the 5-R^F-5-deazaalloxazines reported herein privileged scaffolds for mechanism- and fragment-based drug design. At the same time, the possibility to reduce the pyridine fragment of pyrimido[4,5-*b*]quinoline-2,4(3*H*,10*H*)-dione is a crucial feature important for the development of artificial analogues of the NADH/NAD^+ reductive/oxidative system with a tunable redox potential. This is relevant for biocatalysis and structural biochemistry as well as for the design and construction of new FAD-like redox-systems. On the other hand, the combinatorial aspect of our synthetic strategies can be used in other fields of biology-oriented syntheses.[29] In the future, we plan to study the synthesis of 5-R^F-5-deazaflavins as well as polyfluorinated analogues of riboflavin (vitamin B_2) containing sugars or sugar mimicking fragments located at position 10.

Experimental

General procedure for the synthesis of 6-anilino-5-(polyfluoroacyl)-1,3-dialkyluracils (3)

To a solution of the corresponding 6-amino-1,3-dialkyluracil **2** (0.4 g) in 4 mL of dry dioxane was added pyridine (1.2 equiv.) and the corresponding anhydride (or chloroanhydride if R^F = *n*-C_3F_7) of polyfluorocarboxylic acid (2 equiv.). Then the reaction mixture was allowed to stand at r.t. overnight. The next day the solvent was evaporated, the residue was dried under high vacuum at 100 °C and the crude product **2** was triturated with water, filtered off by suction and dried under a high vacuum.

6-(4-Ethoxyanilino)-1,3-dimethyl-5-(trifluoroacetyl)uracil (3q). Yield 82%, brownish solid, mp 142 °C. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 1.36 (t, 3H, ^3J = 7.0 Hz, Me), 3.03 (s, 3H, Me), 3.22 (s, 3H, Me), 4.07 (q, 2H, ^3J = 7.0 Hz, CH_2O), 7.00 (d, 2H, ^3J = 8.9 Hz, Ar), 7.29 (d, 2H, ^3J = 8.9 Hz, Ar), 11.34 (br s, 1H, NH); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 15.4 (Me), 28.6 (Me), 36.3 (Me), 64.3 (CH_2), 92.7 (C-5), 116.1 (CH), 117.9 (q, $^1J_{C,F}$ = 287.9 Hz, CF_3), 126.3 (CH), 131.5, 151.7, 157.9, 159.4, 160.6, 178.4 (q, $^2J_{C,F}$ = 35.7 Hz, CO); MS (GC, 70 eV): *m*/*z* (%) = 371 ([M]$^+$, 11), 353 (10), 276 (21), 275 (100), 274 (19), 247 (10), 246 (73), 189 (16), 162 (10), 161 (14), 148 (20), 147 (22), 134 (15), 133 (15), 132 (17), 82 (24); HRMS (EI): calcd for $C_{16}H_{16}F_3N_3O_4$ [M]$^+$: 371.10874, found: 371.10840; IR (ATR, cm^{-1}): ν = 2982 (w), 1722 (m), 1668 (s), 1614 (s), 1576 (s), 1504 (s), 1485 (s), 1454 (s), 1441 (s), 1408 (m), 1389 (m), 1315 (s), 1304 (m), 1281 (m), 1257 (s), 1242 (s), 1211 (s), 1188 (s), 1169 (s), 1151 (s), 1113 (s), 1080 (s), 1045 (s), 995 (s), 957 (m), 932 (m), 922 (m), 874 (m), 833 (s), 824 (m), 795 (s), 758 (s), 737 (s), 721 (m), 689 (s), 656 (s), 633 (m), 586 (m), 567 (s), 534 (m).

General procedure for the synthesis of 1,3-dialkyl-5-(polyfluoroalkyl)pyrimido[4,5-*b*]quinoline-2,4-diones (4)

The corresponding uracil **3** (0.3 g) was dissolved in concentrated H_2SO_4 (1.5 mL) and allowed to stand at r.t. for 3 h. Then the solution was poured into ice water and the formed precipitate was filtered off by suction and recrystallized from methanol giving the pure product **4**.

1,3-Dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione (4a). Yield 89%, yellow solid, mp 195 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 3.52 (s, 3H, Me-3), 3.83 (s, 3H, Me-1), 7.55–7.62 (m, 1H, H-7), 7.81–7.89 (m, 1H, H-8), 8.01–8.06 (m, 1H, H-9), 8.30–8.36 (m, 1H, H-6); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 29.4 (Me-3), 30.6 (Me-1), 110.4 (C-4a), 121.7, 123.3 (q, $^1J_{C,F}$ = 278.7 Hz, CF_3), 126.1 (q, $^4J_{C,F}$ = 6.1 Hz, C-6), 127.2, 129.1 (CH), 133.4 (CH), 138.7 (q, $^2J_{C,F}$ = 33.4 Hz, C-5), 148.2, 150.2, 151.1 (CO-2), 159.3 (CO-4); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −52.5 (s, CF_3); MS (GC, 70 eV): *m*/*z* (%) = 310 ([M + H]$^+$, 13), 309 ([M]$^+$, 77), 197 (100); HRMS (ESI): calcd for $C_{14}H_{11}F_3N_3O_2$ [M + H]$^+$: 310.07979, found: 310.07967; IR (ATR, cm^{-1}): ν = 2956 (w), 1713 (s), 1669 (s), 1614 (w), 1583 (s), 1565 (m), 1494 (m), 1464 (s), 1419 (m), 1378 (s), 1332 (m), 1286 (m), 1216 (m), 1194 (m), 1156 (s), 1142 (s), 1124 (s), 1100 (s), 1069 (m), 1030 (m), 989 (s), 929 (w), 877 (w), 856 (w), 812 (m), 775 (s), 756 (s), 745 (s), 712 (w), 624 (s), 592 (m), 550 (m), 532 (w).

General procedure for the synthesis of 5-hydroxy-1,3-dimethyl-5-(perfluoroalkyl)-5,10-dihydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-diones (6)

The corresponding uracil **5** (1.0 g) was dissolved in concentrated H_2SO_4 (5 mL) and allowed to stand at r.t. for 2 h. Then the solution was poured into ice water and extracted with chloroform, dried over Na_2SO_4 and evaporated by rotovap. The crude product was purified *via* short-part column chromatography (silica gel/$CHCl_3$), followed by recrystallization from methanol.

5-Hydroxy-1,3,10-trimethyl-5-(trifluoromethyl)-5,10-dihydropyrimido[4,5-*b*]quinoline-2,4(1*H*,3*H*)-dione (6c). Yield 72%, white solid, mp 216–218 °C. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 3.26 (s, 3H, Me), 3.48 (s, 3H, Me), 3.51 (s, 3H, Me), 7.32 (dd, 1H, ^3J = 7.7, 7.2 Hz, H-7), 7.46 (d, 1H, ^3J = 8.3 Hz, H-9), 7.6 (dd, 1H, ^3J = 8.3, 7.2 Hz, H-8), 7.67 (d, 1H, ^3J = 7.7 Hz, H-6), 8.45 (br s, 1H, OH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 28.5 (Me), 37.3 (Me), 41.8 (Me), 71.8 (q, $^2J_{C,F}$ = 30.5 Hz), 88.1 (C-4a), 119.3 (CH), 125.2 (CH), 126.2 (q, $^1J_{C,F}$ = 290.5 Hz, CF_3), 126.7 (CH), 130.8 (CH), 141.7, 152.4, 153.3, 165.0; ^{19}F NMR (282.4 MHz, DMSO-d_6): δ = −83.1 (s, CF_3); MS (EI, 70 eV): *m*/*z* (%) = 273 (41), 272 (100), 257 (10); HRMS (ESI): calcd for $C_{15}H_{15}F_3N_3O_3$ [M + H]$^+$: 342.10600, found: 342.10635; IR (ATR, cm^{-1}): ν = 3271 (w), 3190 (w), 2980 (w), 1703 (s), 1687 (m), 1622 (s), 1608 (s), 1574 (m), 1504 (s), 1487 (s), 1470 (s), 1464 (s), 1456 (s), 1423 (s), 1396 (m), 1381 (m), 1323 (m), 1254 (s), 1207 (m), 1161 (s), 1119 (s), 1090 (m), 1070 (s), 1049 (s), 972 (m), 955 (w), 937 (m), 922 (s), 866 (w), 833 (m), 779 (s), 768 (s), 760 (s), 746 (s), 710 (s), 662 (s), 642 (s), 602 (m), 565 (m), 550 (m), 538 (m).

Addition of acetophenone to 1,3-dimethyl-5-(trifluoromethyl)-pyrimido[4,5-*b*]quinoline-2,4-diones 4f and 7a. Synthesis of compounds 12a and 13a

Into a flask were placed compound **4f** or **7a** (1 equiv.), acetophenone (1.5 equiv.), dry THF (20 mL per 1.0 g of starting material) and sodium hydride (60% in mineral oil, 2 equiv.). The reaction mixture was stirred for half an hour at r.t. and then allowed to stand overnight. Afterwards 2.5 equiv. of acetic acid was added and the mixture was diluted with water. The formed precipitate was filtered off by suction, washed with heptane and recrystallized from methanol–water giving the pure product.

8,10-Dimethyl-6-phenacyl-6-(trifluoromethyl)-1,2-dihydro-6*H*-pyrimido[4,5-*b*]pyrrolo[3,2,1-*ij*]quinoline-7,9(8*H*,10*H*)-dione (13a). Yield 93%, white solid, mp 304–305 °C. ^{1}H NMR (250.1 MHz, $CDCl_3$): δ = 3.18 (s, 3H, Me), 3.20–3.44 (m, 2H, CH_2-2), 3.64 (s, 3H, Me), 3.85 (d, 1H, ^2J = 18.4 Hz, C*H*HCO), 4.00–4.14 (m, 1H, C*H*H-1), 4.54–4.65 (m, 1H, CH*H*-1), 5.63 (d, 1H, ^2J = 18.4 Hz, CH*H*CO), 7.00 (dd, 1H, ^3J = 7.2, 8.1 Hz, H-4), 7.11–7.19 (m, 2H, Ar), 7.39–7.49 (m, 2H, Ph), 7.54 (t, 1H, ^3J = 7.3 Hz, Ph), 7.91–7.98 (m, 2H, Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.5 (Me), 28.9 (CH_2), 38.4 (CH_2), 38.6 (Me), 47.8 (q, $^2J_{C,F}$ = 26.7 Hz,

C-5), 53.4 (CH_2), 84.7 (C-6a), 117.6, 124.4 (CH), 124.8 (CH), 125.0 (CH), 127.5 (q, $^1J_{C,F}$ = 286.6 Hz, CF_3), 128.2 (CH), 128.8, 128.9 (CH), 133.3, 137.2, 141.8, 152.9, 152.9, 162.0, 195.7; ^{19}F NMR (235.3 MHz, $CDCl_3$): δ = −76.8 (s, CF_3); MS (GC, 70 eV): m/z (%) = 455 ([M]$^+$, 5.8), 387 (26), 386 (100), 336 (15), 105 (38), 77 (14); HRMS (ESI): calcd for $C_{24}H_{21}F_3N_3O_3$ [M + H]$^+$: 456.15295, found: 456.15399; IR (ATR, cm^{-1}): ν = 3043 (w), 3016 (w), 2929 (w), 1691 (s), 1633 (s), 1626 (s), 1539 (s), 1498 (s), 1464 (s), 1446 (s), 1435 (s), 1408 (s), 1375 (s), 1360 (s), 1342 (m), 1302 (m), 1242 (s), 1227 (s), 1201 (m), 1186 (m), 1176 (m), 1155 (s), 1120 (s), 1078 (m), 1057 (m), 1041 (m), 1028 (m), 1001 (m), 976 (m), 964 (m), 939 (m), 912 (m), 897 (w), 860 (w), 847 (w), 779 (s), 770 (m), 756 (s), 748 (s), 737 (s), 714 (m), 694 (s), 658 (m), 617 (s), 581 (m), 569 (m), 528 (m).

Addition of hydrogen cyanide to 1,3-dimethyl-5-(trifluoromethyl)pyrimido[4,5-*b*]quinoline-2,4-diones 4f and 7a. Synthesis of compounds 12c and 13c

Compound **4f** or **7a** (1 equiv.) was suspended in DMSO and KCN (2 equiv.) was added. Then the reaction mixture was stirred overnight and acetic acid (2 equiv.) was carefully added under a fume hood. Afterwards the mixture was diluted with water and the formed precipitate was filtered off by suction and recrystallized from methanol–water giving the pure product.

7-Ethyl-1,3-dimethyl-2,4-dioxo-5-(trifluoromethyl)-1,2,3,4,5,10-hexahydropyrimido[4,5-*b*]quinoline-5-carbonitrile (12c). Yield 94%, white solid, mp 179 °C. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 1.22 (t, 3H, ^3J = 7.6 Hz, Me), 2.70 (q, 2H, ^3J = 7.6 Hz, CH_2), 3.26 (s, 3H, Me), 3.54 (s, 3H, Me), 7.43 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.8 Hz, H-8), 7.51 (d, 1H, ^3J = 8.4 Hz, H-9), 7.53 (s, 1H, H-6), 9.96 (br s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 16.4 (Me), 28.3 (CH_2), 28.8 (Me), 31.4 (Me), 46.3 (q, $^2J_{C,F}$ = 31.9 Hz, C-5), 74.5 (C-4a), 112.6, 115.9, 118.7 (CH), 124.8 (q, $^1J_{C,F}$ = 289.3 Hz, CF_3), 128.4 (CH), 131.7 (CH), 134.6, 141.0, 148.3, 151.0, 160.4; ^{19}F NMR (282.4 MHz, DMSO-d_6): δ = −75.1 (s, CF_3); MS (EI, 70 eV): m/z (%) = 364 ([M]$^+$, 1.03), 338 (17), 337 ([M − HCN]$^+$, 97), 322 (27), 309 (11), 296 (10), 295 (53), 280 (11), 268 (19), 265 (23), 239 (10), 238 (16), 237 (11), 226 (12), 225 (100), 224 (13), 210 (17), 196 (11); HRMS (ESI): calcd for $C_{17}H_{16}F_3N_4O_2$ [M + H]$^+$: 365.12199, found: 365.12186; IR (ATR, cm^{-1}): ν = 3526 (w), 3326 (m), 2977 (w), 1688 (m), 1633 (m), 1613 (s), 1601 (m), 1531 (s), 1502 (s), 1472 (s), 1435 (s), 1414 (m), 1392 (w), 1368 (w), 1338 (w), 1300 (w), 1260 (w), 1232 (w), 1218 (m), 1180 (s), 1159 (m), 1145 (m), 1101 (w), 1068 (w), 1035 (m), 1002 (w), 965 (m), 940 (w), 894 (w), 866 (w), 835 (s), 771 (m), 759 (m), 733 (w), 706 (w), 692 (w), 661 (w), 577 (m), 565 (m), 545 (m), 531 (w).

Notes and references

1 R. B. Silverman, *The Organic Chemistry of Drug Design, and Drug Action*, Elsevier Academic Press, 2nd edn, 2004, p. 617, ISBN 0-12-643732-7.
2 M. Palmer, J. F. Honek and T. Dieckmann, *Biochemical Pharmacology*, John Wiley & Sons, 1st edn, 2012, p. 428, ISBN-13: 978-0-470-17445-6.
3 J.-P. Begue and D. Bonnet-Delpont, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, 1st edn, 2008, p. 366, ISBN-10: 0470278307.
4 (*a*) A. Ohno, J. Kunitomo, Y. Kawai, T. Kawamoto, M. Tomishima and F. Yoneda, *J. Org. Chem.*, 1996, **61**, 9344–9355; (*b*) F. Yoneda, K. Mori, Y. Sakuma and H. Yamaguchi, *J. Chem. Soc., Perkin Trans. 1*, 1980, 978–981; (*c*) T. Nagamatsu, Y. Hashiguchi, M. Higuchi and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 1982, 1085–1086; (*d*) K. Mori, K. Shinozuka, Y. Sakuma and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 1978, 764.
5 F. Yoneda and Y. Sakuma, *J. Chem. Soc., Chem. Commun.*, 1977, 825–826.
6 (*a*) H.-J. Duchstein, H. Fenner, P. Frank and W. Bauch, *Arch. Pharm.*, 1990, **323**, 67–72; (*b*) H.-J. Duchstein, H. Fenner and W. Bauch, *Arch. Pharm.*, 1989, **322**, 271–275.
7 (*a*) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123–3197; (*b*) P. Lin and J. Jiang, *Tetrahedron*, 2000, **56**, 3635–3671; (*c*) G. Resnati, *Tetrahedron*, 1993, **49**, 9385–9445.
8 T. Hiyama, *Organofluorine Compounds: Chemistry and Application*, Springer, Berlin, 2000.
9 (*a*) V. O. Iaroshenko, D. V. Sevenard, A. V. Kotljarov, D. M. Volochnyuk, A. O. Tolmachev and V. Y. Sosnovskikh, *Synthesis*, 2009, 731–740; (*b*) V. O. Iaroshenko, *Synthesis*, 2009, 3967–3974; (*c*) V. O. Iaroshenko, D. Ostrovskyi, A. Petrosyan, S. Mkrtchyan, A. Villinger and P. Langer, *J. Org. Chem.*, 2011, **76**, 2899–2903.
10 (*a*) G. Cristalli, S. Costanzi, C. Lambertucci, G. Lupidi, S. Vittori, R. Volpini and E. Camaioni, *Med. Res. Rev.*, 2001, **21**, 105–128; (*b*) O. Maydanovych and P. A. Beal, *Chem. Rev.*, 2006, **106**, 3397–3411; (*c*) E. Santaniello, P. Ciuffreda and L. Alessandrini, *Synthesis*, 2005, 509–526.
11 (*a*) G. Cristalli, S. Costanzi, C. Lambertucci, G. Lupidi, S. Vittori, R. Volpini and E. Camaioni, *Med. Res. Rev.*, 2001, **21**, 105–128; (*b*) V. Nair, *IMPDH Inhibitors: Discovery of Antiviral Agents Against Emerging Diseases in Antiviral Drug Discovery for Emerging Diseases and Bioterrorism Threats*, ed. P. F. Torrence, John Wiley & Sons, Inc., Hoboken, 2005, ch. 8, pp. 179–202; (*c*) Q. Shu and V. Nair, *Med. Res. Rev.*, 2008, 219–232; (*d*) M. D. Erion and M. R. Reddy, *J. Am. Chem. Soc.*, 1998, **120**, 3295–3307; (*e*) L. Hedstrom, *Chem. Rev.*, 2009, **109**, 2903–2928.
12 (*a*) K. Senga, F. Yoneda and S. Nishigaki, *J. Org. Chem.*, 1971, **36**, 1829–1831; (*b*) S. Wawzonek, *J. Org. Chem.*, 1976, **41**, 3149–3151; (*c*) F. Yoneda, F. Takayama and A. Koshiro, *Chem. Pharm. Bull.*, 1979, **27**, 2507–2510; (*d*) K. Hirota, K. Kubo, H. Sajiki, Y. Kitade, M. Sako and Y. Maki, *J. Org. Chem.*, 1997, **62**, 2999–3001; (*e*) A. Chandra, S. Upadhyay, B. Singh, N. Sharma and R. M. Singh, *Tetrahedron*, 2011, **67**, 9219–9224.
13 Z. Wang and C. J. Rizzo, *Org. Lett.*, 2000, **2**, 227–230.
14 (*a*) F. Yoneda, Y. Sakuma, S. Mizumoto and R. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1805–1808; (*b*) P. A. J. Link,

H. C. van der Plas and F. Müller, *J. Heterocycl. Chem.*, 1985, **22**, 841–848; (*c*) P. A. J. Link, P. H. C. van der Plas and F. Müller, *J. Heterocycl. Chem.*, 1985, **22**, 873–878; (*d*) Y. Tominaga, H. Okuda, N. Tochiki, Y. Natsuda and G. Kobayashi, *Heterocycles*, 1981, **15**, 679–683; (*e*) R. W. Grauert, *Arch. Pharm.*, 1982, **315**, 949–958; (*f*) J. Trilleras, L. G. López, D. J. Pacheco, J. Quiroga, M. Nogueras, J. M. de la Torre and J. Cobo, *Molecules*, 2010, **15**, 7227–7234; (*g*) J. Quiroga, J. Trilleras, B. Insuasty, R. Abonía, M. Nogueras, A. Marchal and J. Cobo, *Tetrahedron Lett.*, 2010, **51**, 1107–1109; (*h*) R. N. Kumar, T. Suresh, A. Mythili and P. S. Mohan, *Heterocycl. Commun.*, 2001, **7**, 193–198.

15 (*a*) S. Nishigaki, J. Sato, K. Shimizu, K. Furukawa, K. Senga and F. Yoneda, *Chem. Pharm. Bull.*, 1980, **28**, 142–149; (*b*) K. Aknin, S. Desbène-Finck, P. Helissey and S. Giorgi-Renault, *Mol. Divers.*, 2010, **14**, 123–130.

16 K. Aknin, S. Desbène-Finck, P. Helissey and S. Giorgi-Renault, *Mol. Divers.*, 2010, **14**, 123–130.

17 (*a*) V. P. Khilya, L. G. Grishko, L. I. Shevchenko, L. I. Barvinok, V. A. Dymovich and V. Sabo, *Chem. Heterocycl. Compd.*, 1973, **9**, 1091–1097; (*b*) M. Takahashi, K. Akiyama, T. Suzuki and H. Inoue, *J. Heterocycl. Chem.*, 2008, **45**, 601–605; (*c*) S. V. Druzhinin, E. S. Balenkova and V. G. Nenajdenko, *Tetrahedron*, 2007, **63**, 7753–7808; (*d*) V. Y. Sosnovskikh, *Russ. Chem. Rev.*, 2003, **72**, 489–516.

18 Q. Dong, V. Feher, S. W. Kaldor and N. Tomita, *US*, 2008/0125437.

19 (*a*) H. Biltz and H. Wittek, *Chem. Ber.*, 1921, **54**, 1035–1058; (*b*) W. Pfleiderer and K.-H. Schündehütte, *Liebigs Ann. Chem.*, 1958, **612**, 158–163.

20 Crystallographic data (excluding structure factors) for the structures **4j**, **4m**, **4q**, **6a**, **7a**, **8a**, **9** and **13** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 895395–895401 and CCDC 934983.

21 B. A. Vigante, Y. Y. Oyols, B. S. Chekavichus and G. Y. Dubur, *Khim. Geterotsikl. Soedin.*, 1987, **9**, 1232–1238.

22 I. P. Beletskaya, A. V. Tsvetkov, P. V. Tsvetkov and G. V. Latyshev, *Russ. Chem. Bull.*, 2005, **54**, 215–219.

23 N. S. Gulykina, T. M. Dolgina, G. N. Bondarenko and I. P. Beletskaya, *Russ. J. Org. Chem.*, 2003, **39**, 797–807.

24 W. Verboom, D. N. Reinhoudt, S. Harkema and G. I. van Hummel, *J. Org. Chem.*, 1982, **47**, 3339–3342.

25 (*a*) W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1982, **47**, 3339–3342; (*b*) M. Hojo, R. Masuda and E. Okada, *Tetrahedron Lett.*, 1988, **29**, 4599–4602.

26 E. Okada, R. Masuda, M. Hojo and T. Tomifuji, *Heterocycles*, 1993, **36**, 845–856.

27 I. D. Jurberg, B. Peng, E. Wöstefeld, M. Wasserloos and N. Maulide, *Angew. Chem., Int. Ed.*, 2012, **51**, 1950–1953.

28 N. Kaval, B. Halasz-Dajka, G. Vo-Thanh, W. Dehaen, J. van der Eycken, P. Mátyus, A. Loupy and E. van der Eycken, *Tetrahedron*, 2005, **61**, 9052–9057.

29 S. Wetzel, R. S. Bon, K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 10800–10826.